ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

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ABSTRACT

BACKGROUND

The bedaquiline–pretomanid–linezolid regimen has been reported to have 90% efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with 1200 mg of linezolid daily has been high. The appropriate dose of linezolid and duration of treatment with this agent to minimize toxic effects while maintaining efficacy against highly drug-resistant tuberculosis are unclear.

METHODS

We enrolled participants with extensively drug-resistant (XDR) tuberculosis (i.e., resistant to rifampin, a fluoroquinolone, and an aminoglycoside), pre-XDR tuberculosis (i.e., resistant to rifampin and to either a fluoroquinolone or an aminoglycoside), or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. We randomly assigned the participants to receive bedaquiline for 26 weeks (200 mg daily for 8 weeks, then 100 mg daily for 18 weeks), pretomanid (200 mg daily for 26 weeks), and daily linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks. The primary end point in the modified intention-to-treat population was the incidence of an unfavorable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. Safety was also evaluated.

RESULTS

A total of 181 participants were enrolled, 88% of whom had XDR or pre-XDR tuberculosis. Among participants who received bedaquiline–pretomanid–linezolid with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91%, and 84%, respectively, had a favorable outcome; peripheral neuropathy occurred in 38%, 24%, 24%, and 13%, respectively; myelosuppression occurred in 22%, 15%, 2%, and 7%, respectively; and the linezolid dose was modified (i.e., interrupted, reduced, or discontinued) in 51%, 30%, 13%, and 13%, respectively. Optic neuropathy developed in 4 participants (9%) who had received linezolid at a dose of 1200 mg for 26 weeks; all the cases resolved. Six of the seven unfavorable microbiologic outcomes through 78 weeks of follow-up occurred in participants assigned to the 9-week linezolid groups.

CONCLUSIONS

A total of 84 to 93% of the participants across all four bedaquiline–pretomanid–linezolid treatment groups had a favorable outcome. The overall risk–benefit ratio favored the group that received the three-drug regimen with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications. (Funded by the TB Alliance and others; ZeNix ClinicalTrials.gov number, NCT03086486.)

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*A list of the ZeNix Trial Team members is provided in the Supplementary Appendix, available at NEJM.org.

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Drug-resistant tuberculosis remains a driving factor behind the worldwide tuberculosis epidemic, and shorter, safer, and more effective treatment regimens are needed.[1] In 2020, a total of 157,903 cases of rifampin-resistant tuberculosis were reported, and 25,681 of these cases involved additional resistance to core drugs (i.e., levofloxacin or moxifloxacin, bedaquiline, and linezolid), although this case count is probably an underestimate.[2] Currently, treatment lasts between 9 and 24 months and involves multiple drugs that have serious side effects, including cardiac toxic effects, neuropathy, and liver dysfunction.[3]

Within the past decade, the approval of several drugs for the treatment of drug-resistant tuberculosis has heralded a new era in treatment. Bedaquiline, a diarylquinoline, inhibits mycobacterial ATP synthase and is licensed for use in the treatment of drug-resistant tuberculosis.[4] Pretomanid is a nitroimidazooxazine with activity against replicating and dormant mycobacteria through inhibition of mycolic acid biosynthesis and nitric oxide release, respectively.[5,6] Linezolid is a repurposed oxazolidinone that inhibits mycobacterial protein synthesis,[7] but its prolonged use is associated with peripheral neuropathy and myelosuppression.[8,9]

In the Nix-TB study,[10] 90% of the patients with highly drug-resistant tuberculosis who received bedaquiline, pretomanid, and linezolid for 26 weeks had a favorable outcome. However, the use of linezolid at a dose of 1200 mg daily was associated with a high incidence of adverse events. Here, we present the results of the ZeNix trial, which was designed to investigate the efficacy and safety of different doses of linezolid in the bedaquiline–pretomanid–linezolid regimen for highly drug-resistant tuberculosis.

Methods

Trial Design

ZeNix was a partially blind, randomized trial that enrolled participants with pulmonary extensively drug-resistant (XDR) tuberculosis, pre-XDR tuberculosis, or rifampin-resistant tuberculosis. Participants with XDR tuberculosis had resistance to rifampin, a fluoroquinolone, and an aminoglycoside. Pre-XDR tuberculosis was defined as resistance to rifampin plus resistance to either a fluoroquinolone or an aminoglycoside. Rifampin-resistant tuberculosis was defined as *Mycobacterium tuberculosis* that was resistant to rifampin (with or without resistance to isoniazid) and did not respond to treatment or for which a second-line regimen had been discontinued because of side effects 6 months or more before enrollment.

A Quick Take is available at NEJM.org

All the participants received treatment for 26 weeks, with the option to extend treatment to 39 weeks if ongoing active disease was suspected between weeks 16 and 26. The full trial protocol is available with the full text of this article at NEJM.org.

Trial Participants

Participants were recruited from four trial sites in South Africa, one in the country of Georgia, one in Moldova, and five in Russia. The participants were 14 years of age or older (≥18 years of age in Russia and Moldova) and had had a documented positive sputum culture or molecular test for *M. tuberculosis* within 3 months before screening.

Participants were excluded if they had human immunodeficiency virus (HIV) infection and a CD4+ cell count of less than 100 per cubic millimeter; a risk of arrhythmia; an alanine aminotransferase level and an aspartate aminotransferase level higher than 3 times the upper limit of the normal range; or peripheral neuropathy of grade 3 or higher at baseline. Participants were excluded if they had previously received any of the three trial drugs or delamanid for 2 weeks or more before enrollment. The full inclusion and exclusion criteria are provided in Section S5. All the participants provided written informed consent.

Enrollment and Interventions

The participants were randomly assigned, in a 1:1:1:1 ratio, to one of the four linezolid regimens (either 1200 mg or 600 mg daily for either 26 weeks or 9 weeks) by trial site staff using an online portal. Randomization was stratified according to HIV status and classification of drug resistance.

In addition to linezolid, all participants received 26 weeks of bedaquiline (200 mg daily for 8 weeks, followed by 100 mg daily for 18 weeks) and pretomanid (200 mg daily for 26 weeks).

The dose of linezolid could be reduced in a stepwise manner (1200 mg, 600 mg, 300 mg, or 0 mg) in response to adverse events. The participants, site staff, and trial team were unaware of the assigned duration and dose of linezolid treatment (see Section 4 in the protocol); matched placebo was provided for blinding. Adherence was monitored by direct observation if the participant was in the hospital or by checking medication cards and bottles for unused tablets at site visits.

Scheduled visits occurred weekly for the first 8 weeks, every 2 weeks until week 20, and then every 3 weeks until the end of treatment. The participants were followed for a minimum of 78 weeks after the completion of treatment, with scheduled visits in the follow-up period.

MICROBIOLOGIC ASSESSMENTS

At the screening visit, two sputum samples were obtained for smear microscopy, molecular testing for rifampin resistance (with the use of the Xpert MTB/RIF [Cepheid] or GenoType MTBDRplus assay [Hain Lifescience]), and culture in liquid medium in a Mycobacterial Growth Indicator Tube (MGIT) system (Becton Dickinson). Samples for culture in the MGIT system were then obtained weekly for 4 weeks and at weeks 6, 8, 10, 12, 16, 20, 23, and 26, and at each follow-up visit after the completion of treatment.

M. tuberculosis isolates from baseline cultures and the first positive culture on or after week 16 in participants who did not have a response to treatment were sent to a central laboratory for the determination of the MGIT minimum inhibitory concentration (MIC) of bedaquiline, pretomanid, and linezolid; for MGIT drug-susceptibility testing for first-line drugs (rifampin, isoniazid, pyrazinamide, ethambutol, and streptomycin), kanamycin, and moxifloxacin; and for whole-genome sequencing. *M. tuberculosis* isolates from participants with recurrence of tuberculosis were analyzed with the use of whole-genome sequencing[11] to distinguish between relapse and reinfection. For all drugs except pretomanid, the critical concentrations recommended by the World Health Organization were used to define resistance.[12] *M. tuberculosis* isolates with a pretomanid MIC of greater than 2 mg per liter were considered to be resistant.[13] The laboratory manual, which includes full details of the microbiologic procedures, is provided in Section S15 in the Supplementary Appendix, available at NEJM.org.

SAFETY

Adverse events were recorded at every trial visit, and laboratory safety tests were performed weekly for the first 8 weeks and at scheduled visits during treatment. Electrocardiographic monitoring, examinations to assess color vision and visual acuity, and specific assessments for peripheral neuropathy with the use of a Brief Peripheral Neuropathy rating scale were also performed at scheduled intervals (Section S4 in the Supplementary Appendix).

OUTCOME MEASURES AND END POINTS

The primary end point was the incidence of an unfavorable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. In participants with bacteriologic treatment failure, negative culture status was not attained or maintained during treatment. Clinical treatment failure was defined as one of the following: a change from the protocol-specified tuberculosis treatment as a result of a lack of clinical efficacy, retreatment for tuberculosis, or tuberculosis-related death by 26 weeks after completion of treatment. Culture conversion was defined as at least two consecutive culture-negative samples obtained at least 7 days apart. In participants with relapse, negative culture conversion status was not maintained during follow-up, and a positive culture of an *M. tuberculosis* strain was confirmed as being genetically identical to that at baseline. Participants were considered to have a favorable outcome if they continued to have negative culture status during treatment to the end of follow-up and if they had not already been classified as having had an unfavorable outcome.

Secondary end points included bacteriologic or clinical treatment failure and relapse at 78 weeks after the end of treatment. Other secondary end points were the time to sputum culture conversion and the percentages of participants with culture conversion at specified time points.

Safety evaluations included adverse events,

laboratory measurements, and death from any cause. Adverse events that occurred or worsened during the treatment period were defined as events that occurred between the start of treatment and 14 days after the end of treatment. The severity of adverse events was categorized according to grade, as defined by the Division of Microbiology and Infectious Diseases system,[14] and site investigators provided an assessment of relatedness to trial medications. All the participants who received at least one dose of a trial drug were included in the safety analysis.

TRIAL OVERSIGHT

An independent data and safety monitoring committee reviewed safety and efficacy data throughout the trial. National and local ethics committees approved the trial. The TB Alliance, the trial sponsor, was responsible for the design and conduct of the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

The primary efficacy analysis was conducted with the results of the MGIT culture. We hypothesized that the incidence of cure at 26 weeks after the end of therapy would be greater than 50% in each of the treatment groups. The incidence was estimated from the binomial proportion for participants with success criteria based on the lower boundary of the 95% confidence interval being greater than 50%. The trial did not have a control group.

We determined that a sample of 45 participants per group would provide the trial with more than 90% power to show that the lower boundary of the 95% confidence interval was greater than 50%, using a two-sided 5% significance level (and assuming a true cure rate of 80%). Intention-to-treat, modified intention-to-treat, and per-protocol analyses for each group were conducted (Section S6). The intention-to-treat population was defined as all participants who underwent randomization, with the exception of those who were excluded after the randomization period either because of protocol violations that occurred before randomization (and were detected after randomization) or because they did not have drug-resistant tuberculosis that was confirmed on the basis of a sputum sample obtained within 3 months before screening; the modified intention-to-treat population as the participants in the intention-to-treat population, with the exception of those who were lost to follow-up after successful treatment or who died from a cause that was adjudicated to be unrelated to tuberculosis; and the per-protocol population as the participants in the modified intention-to-treat population, with the exception of those who were excluded for additional protocol-related reasons.

The primary comparison against the target 50% efficacy was for the bedaquiline–pretomanid–linezolid regimen with linezolid at a dose of 1200 mg for 26 weeks, with the group that received 1200 mg of linezolid for 9 weeks and the group that received 600 mg of linezolid for 26 weeks being tested only if 1200 mg for 26 weeks was successful. The group that received 600 mg of linezolid for 9 weeks would be tested only if the dose of 600 mg for 26 weeks was successful. A Bonferroni adjustment was made for the comparison of the group that received 1200 mg of linezolid for 9 weeks with the group that received 600 mg for 26 weeks simultaneously, and 97.5% confidence intervals were reported for these groups. No formal statistical pairwise comparisons between groups were performed.

RESULTS

PARTICIPANTS

A total of 248 participants were screened and 181 participants underwent randomization between November 7, 2017, and December 3, 2019 (Fig. 1). The characteristics of potential participants who were excluded during screening are provided in Table S4. The baseline characteristics of all 181 participants who underwent randomization are shown in Table 1; 122 participants (67%) were male, 115 (64%) were White, and 145 (80%) were HIV-negative. Information on the representativeness of the trial participants is provided in Table S4. In the safety population, a mean of 99.8% of the participants adhered to the trial-drug regimen (Table S1).

Of all 181 participants who underwent randomization, 75 (41.4%) had XDR tuberculosis, 85 (47.0%) had pre-XDR tuberculosis, and 21 (11.6%) had rifampin-resistant tuberculosis. All

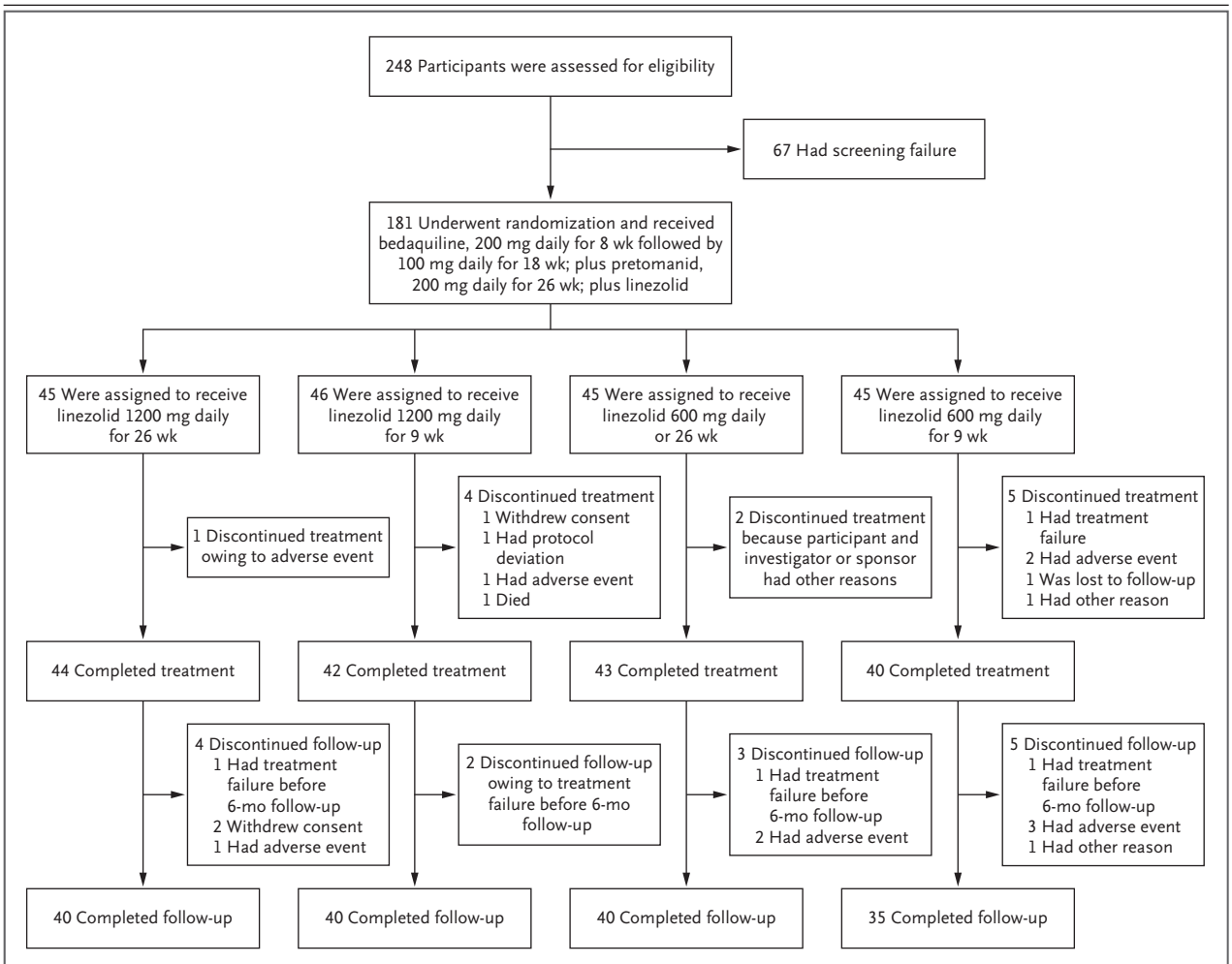

Figure 1. Screening, Randomization, Treatment, and Follow-up.

the participants with rifampin-resistant tuberculosis had resistance to isoniazid, so they were classified as having multidrug-resistant tuberculosis. A total of 11 of 143 participants for whom at least one positive culture between screening and week 4 was analyzed had baseline isolates that were resistant to at least one trial drug.

PRIMARY END-POINT ANALYSIS

Table 2 shows the results of the primary efficacy analysis in the modified intention-to-treat and intention-to-treat populations, and Table S5 shows the outcomes in the per-protocol population. In the modified intention-to-treat analysis, 41 of 44 participants (93%) in the group that received bedaquiline–pretomanid–linezolid with linezolid at a dose of 1200 mg for 26 weeks were classified as having a favorable outcome, as were 40 of 45 participants (89%) in the group that received 1200 mg of linezolid for 9 weeks, 41 of 45 participants (91%) in the group that received 600 mg of linezolid for 26 weeks, and 37 of 44 participants (84%) in the group that received 600 mg of linezolid for 9 weeks. Treatment failure or bacteriologic relapse (confirmed by whole-genome sequencing) accounted for 5 of 19 unfavorable outcomes at 26 weeks of follow-up (Table 2).

Nine participants had baseline phenotypic bedaquiline resistance (two with additional linezolid resistance and one with pretomanid resistance), of whom six (including all three

with dual resistance) had a favorable outcome. The three participants with unfavorable outcomes had received 1200 mg of linezolid for 9 weeks. Two additional participants had baseline pretomanid monoresistant isolates and favorable outcomes.

SECONDARY END-POINT ANALYSIS

In the modified intention-to-treat analysis, favorable outcomes were reported at 78 weeks of follow-up in 40 of 43 participants (93%) who had received bedaquiline–pretomanid–linezolid with linezolid at a dose of 1200 mg for 26 weeks, in 39 of 44 (89%) who had received 1200 mg of linezolid for 9 weeks, in 40 of 45 (89%) who had received 600 mg of linezolid for 26 weeks, and in 35 of 44 (80%) who had received 600 mg of linezolid for 9 weeks. Three participants had unfavorable outcomes at 78 weeks of follow-up, of whom 2 had received 600 mg of linezolid for 9 weeks and had bacteriologic relapse (confirmed by whole-genome sequencing) and 1 had baseline bedaquiline and linezolid resistance. In addition, 1 participant who had received 600 mg of linezolid for 26 weeks was treated again for tuberculosis after 39 weeks of follow-up with no positive cultures. Secondary end-point data in the per-protocol analysis and intention-to-treat analysis were consistent with the data in the modified intention-to-treat analysis (Tables S10 through S12).

Figure 2A shows Kaplan–Meier curves for the time to an unfavorable outcome. The median times to culture conversion were the following: 4 weeks (interquartile range, 2 to 8) in the groups that had received 1200 mg of linezolid for 26 weeks or 9 weeks; 6 weeks (interquartile range, 3 to 8) in the group that had received 600 mg of linezolid for 26 weeks; and 6 weeks (interquartile range, 3 to 10) in the group that had received 600 mg of linezolid for 9 weeks. One participant who had received 600 mg of linezolid for 9 weeks had a treatment extension because of culture-positive sputum between weeks 16 and 26.

SUBGROUP AND SENSITIVITY ANALYSES

In the planned subgroup analyses (Section S12), age, sex, and HIV status did not influence outcomes. The subgroups of participants with a baseline time to positivity above the median and no lung cavities had slightly more favorable outcomes. The results of a sensitivity analysis that excluded participants with negative cultures at baseline were similar to those in the primary efficacy analysis (Tables S13 and S14).

SAFETY ANALYSIS

Safety data are provided in Table 3. At least one adverse event that occurred or worsened during treatment was reported by 156 of 181 participants (86.2%), and serious adverse events that occurred or worsened during treatment were reported by 11 of 181 participants (6.1%). The linezolid dose was modified (interrupted, reduced, or discontinued) in 23 of 45 participants (51%) in the group that had received bedaquiline–pretomanid–linezolid with linezolid at a dose of 1200 mg for 26 weeks and in 14 of 46 (30%) who had received the same dose of linezolid for 9 weeks; in each group that had received 600 mg of linezolid (26 weeks and 9 weeks), 6 of 45 participants (13%) had linezolid dose modifications. Figure 2B shows the time to a first linezolid dose interruption, reduction, or discontinuation. Alterations in the dose were most commonly related to myelosuppression and neuropathy (Tables S23 through S25 and Section S13). One participant in the group that had received 1200 mg of linezolid for 9 weeks died from a methadone overdose.

Peripheral neuropathy of grade 3 or lower was reported in 17 of 45 participants (38%) in the group that had received 1200 mg of linezolid for 26 weeks, in 11 of 46 (24%) in the group that had received 1200 mg of linezolid for 9 weeks, in 11 of 45 (24%) in the group that had received 600 mg of linezolid for 26 weeks, and in 6 of 45 (13%) in the group that had received 600 mg of linezolid for 9 weeks. In all the treatment groups, peripheral neuropathy was reported by a higher percentage of South African participants than of those in Georgia, Moldova, or Russia (Tables S27 and S28). Four participants, all of whom had received 1200 mg of linezolid for 26 weeks, had optic neuropathy that resolved.

Laboratory-confirmed myelosuppression was reported in 10 of 45 participants (22%) in the group that had received bedaquiline–pretomanid–linezolid with linezolid at a dose of 1200 mg for 26 weeks, in 7 of 46 (15%) who had received 1200 mg of linezolid for 9 weeks, in 1 of 45 (2%)

Table 1. Baseline Characteristics of the Participants Who Underwent Randomization.*

Characteristic	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Median age (IQR) — yr	38 (30–44)	33.5 (26–42)	38 (30–46)	36 (32–41)	36 (30–44)
Male sex — no. (%)	30 (67)	30 (65)	31 (69)	31 (69)	122 (67)
Race — no. (%)†					
White	34 (76)	28 (61)	24 (53)	29 (64)	115 (64)
Black	11 (24)	18 (39)	21 (47)	16 (36)	66 (36)
Median weight (IQR) — kg	61.0 (55.0–67.3)	58.9 (52.9–69.0)	61.5 (52.4–66.5)	64.4 (58.0–70.7)	61.2 (54.0–67.8)
Median BMI (IQR)‡	20.3 (18.8–22.3)	21.0 (18.6–23.4)	20.9 (18.6–23.6)	20.8 (19.6–24.0)	20.8 (18.8–23.2)
HIV status — no. (%)					
Positive	9 (20)	9 (20)	9 (20)	9 (20)	36 (20)
Negative	36 (80)	37 (80)	36 (80)	36 (80)	145 (80)
Smoking status — no. (%)					
Never	20 (44)	15 (33)	16 (36)	17 (38)	68 (38)
Current	15 (33)	22 (48)	17 (38)	12 (27)	66 (36)
Former	10 (22)	9 (20)	12 (27)	16 (36)	47 (26)
Diabetes — no. (%)					
Yes§	3 (7)	0	1 (2)	5 (11)	9 (5)
Not reported	42 (93)	46 (100)	44 (98)	40 (89)	172 (95)
Current tuberculosis type — no. (%)¶					
XDR tuberculosis	21 (47)	18 (39)	19 (42)	17 (38)	75 (41)
Pre-XDR tuberculosis	19 (42)	22 (48)	22 (49)	22 (49)	85 (47)
Rifampin-resistant tuberculosis					
Not responsive to treatment	2 (4)	5 (11)	2 (4)	3 (7)	12 (7)
Second-line regimen had been discontinued because of side effects	3 (7)	1 (2)	2 (4)	3 (7)	9 (5)
Cavitation on chest radiography — no. (%)	27 (60)	25 (54)	33 (73)	27 (60)	112 (62)
Median time to positive MGIT at baseline — days	11.1	9.2	9.9	9.3	10.1
IUATLD-WHO smear grade for acid-fast bacilli — no. (%)					
Negative	23 (51)	24 (52)	23 (51)	20 (44)	90 (50)
Scanty positive	11 (24)	4 (9)	8 (18)	5 (11)	28 (15)
1+	4 (9)	7 (15)	4 (9)	6 (13)	21 (12)
2+	6 (13)	6 (13)	3 (7)	4 (9)	19 (10)
3+	1 (2)	5 (11)	7 (16)	10 (22)	23 (13)
Geographic distribution — no. (%)					
South Africa	11 (24)	18 (39)	21 (47)	16 (36)	66 (36)
Georgia, Moldova, or Russia	34 (76)	28 (61)	24 (53)	29 (64)	115 (64)

Table 1. (Continued.)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, IQR interquartile range, IUATLD-WHO International Union against Tuberculosis and Lung Disease–World Health Organization, and MGIT Mycobacterial Growth Indicator Tube.
† Race was reported by the participant.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Shown are the numbers of participants with diabetes indicated on the medical history case-report form.
¶ Extensively drug-resistant (XDR) tuberculosis was defined as *Mycobacterium tuberculosis* that was resistant to rifampin, a fluoroquinolone, and an aminoglycoside. Pre-XDR tuberculosis was defined as *M. tuberculosis* that was resistant to rifampin and to either a fluoroquinolone or an aminoglycoside. Rifampin-resistant tuberculosis was defined as *M. tuberculosis* that was resistant to rifampin (with or without resistance to isoniazid) and did not respond to treatment or for which a second-line regimen had been discontinued because of side effects 6 months or more before enrollment.

who had received 600 mg of linezolid for 26 weeks, and in 3 of 45 (7%) who had received 600 mg of linezolid for 9 weeks. Across the treatment groups, 47 of 181 participants (26%) had one or more liver-related adverse events, with similar numbers in each group. One participant in each group, except the group that had received 1200 mg of linezolid for 26 weeks, reported one or more serious liver-related adverse events.

DISCUSSION

In this randomized trial of four 26-week regimens for highly drug-resistant tuberculosis consisting of daily bedaquiline and pretomanid with different doses and durations of linezolid treatment, the efficacy in all four treatment groups at the primary end point ranged from 84 to 93%. These results are similar to those in the Nix-TB study,[10] and most of the unfavorable outcomes (in 14 of 19 participants) were not related to bacteriologic failure. At 78 weeks of follow-up, two additional relapses had occurred in the group that had received linezolid at a dose of 600 mg for 9 weeks, but no additional relapses had occurred in the other three treatment groups.

Differences were more apparent in linezolid-associated safety measures than in efficacy measures across the treatment groups, with different incidences of peripheral neuropathy, myelosuppression, and linezolid dose modifications. The 600-mg dose of linezolid was associated with fewer linezolid dose modifications, no cases of optic neuropathy, and fewer episodes of peripheral neuropathy and myelosuppression. Unlike the 1200-mg linezolid dose, which had a less favorable safety profile in the 26-week group than in the 9-week group, there was less of a difference between the two 600-mg linezolid groups (26 weeks and 9 weeks). Hematologic toxic effects were uncommon in the two 600-mg linezolid groups. Although peripheral neuropathy that occurred or worsened during treatment occurred more frequently in the group that received linezolid at a dose of 600 mg for 26 weeks, both the 9-week group and the 26-week group had the same incidence (13%) of linezolid dose modifications.

The favorable side-effect profile of the 600-mg dose of linezolid and the lower incidence of bacteriologic failure in the group that received linezolid at a dose of 600 mg for 26 weeks (1 of 45 participants) than in the group that received the same dose of linezolid for 9 weeks (4 of 45 participants) suggest that the 600-mg, 26-week regimen had the most favorable risk–benefit profile among the four regimens studied. This regimen had efficacy that was similar to that previously observed in the Nix-TB study but fewer toxic effects. The more favorable risk–benefit ratio of this 26-week, three-drug, all-oral regimen is a welcome finding for the treatment of highly drug-resistant tuberculosis, which typically involves more drugs and longer treatment.

M. tuberculosis is adept at developing resistance if it is treated with an insufficient number of drugs.[15,16] In this trial, 11 of 143 participants for whom at least one positive culture between screening and week 4 was analyzed had baseline isolates that were resistant to at least one trial drug. Although most of these 11 participants had a favorable outcome, the 3 participants with an unfavorable microbiologic outcome all had

Table 2. Primary End-Point Efficacy Analysis.*

Population and Outcome	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Modified intention-to-treat population					
Not assessable					
Violent or accidental death during treatment period — no.	0	1	0	0	1
Lost to follow-up during follow-up period — no.	1	0	0	0	1
Withdrawn for other reason during follow-up period — no.	0	0	0	1	1
All participants — no. (%)	1 (2)	1 (2)	0	1 (2)	3 (2)
Assessable — no. (%)	44 (98)	45 (98)	45 (100)	44 (98)	178 (98)
Favorable outcome — no./total no. (%)	41/44 (93)	40/45 (89)	41/45 (91)	37/44 (84)	159/178 (89)
95% CI for favorable outcome — %	81–99	76–96	79–98	70–93	84–93
97.5% CI for favorable outcome — %	—	74–97	77–98	—	—
Unfavorable outcome — no./total no. (%)	3/44 (7)	5/45 (11)	4/45 (9)	7/44 (16)	19/178 (11)
Confirmed relapse during follow-up period — no.†	0	2	1	1	4
Lost to follow-up during treatment period — no.	0	0	0	1	1
Retreatment during follow-up period — no.‡	2	0	1	1	4
Withdrawn during treatment period — no.					
Because of adverse event	1	1	0	2	4
Because of investigator or sponsor decision	0	0	1	0	1
Because of participant decision	0	2	1	1	4
Treatment failure during treatment period†	0	0	0	1	1
Intention-to-treat population					
Not assessable — no. (%)	0	0	0	0	0
Assessable — no. (%)	45 (100)	46 (100)	45 (100)	45 (100)	181 (100)
Favorable outcome — no./total no. (%)	41/45 (91)	40/46 (87)	41/45 (91)	37/45 (82)	159/181 (88)
95% CI for favorable outcome — %	79–98	74–95	79–98	68–92	82–92

97.5% CI for favorable outcome — %	—	72–96	77–98	—	—
Unfavorable outcome — no./total no. (%)	4/45 (9)	6/46 (13)	4/45 (9)	8/45 (18)	22/181 (12)
Confirmed relapse during follow-up period — no.†	0	2	1	1	4
Died during treatment period — no.	0	1	0	0	1
Lost to follow-up during follow-up period — no.	1	0	0	1	2
Retreatment during follow-up period — no.‡	2	0	1	1	4
Treatment failure during treatment period — no.†	0	0	0	1	1
Withdrawn during treatment period — no.					
Because of adverse event	1	1	0	2	4
Because of investigator or sponsor decision	0	0	1	0	1
Because of participant decision	0	2	1	1	4
Withdrawn for other reason in follow-up period — no.	0	0	0	1	1

* The intention-to-treat population was defined as all participants who underwent randomization, with the exception of those who were excluded after the randomization period either because of protocol violations that occurred before randomization (and were detected after randomization) or because they did not have drug-resistant tuberculosis that was confirmed on the basis of a sputum sample obtained within 3 months before screening, and the modified intention-to-treat population as the participants in the intention-to-treat population, with the exception of those who were lost to follow-up after successful treatment or who died from a cause that was adjudicated to be unrelated to tuberculosis. CI denotes confidence interval.

† This outcome was unfavorable because of bacteriologically confirmed treatment failure or relapse.

‡ This outcome was unfavorable because of clinical treatment failure.

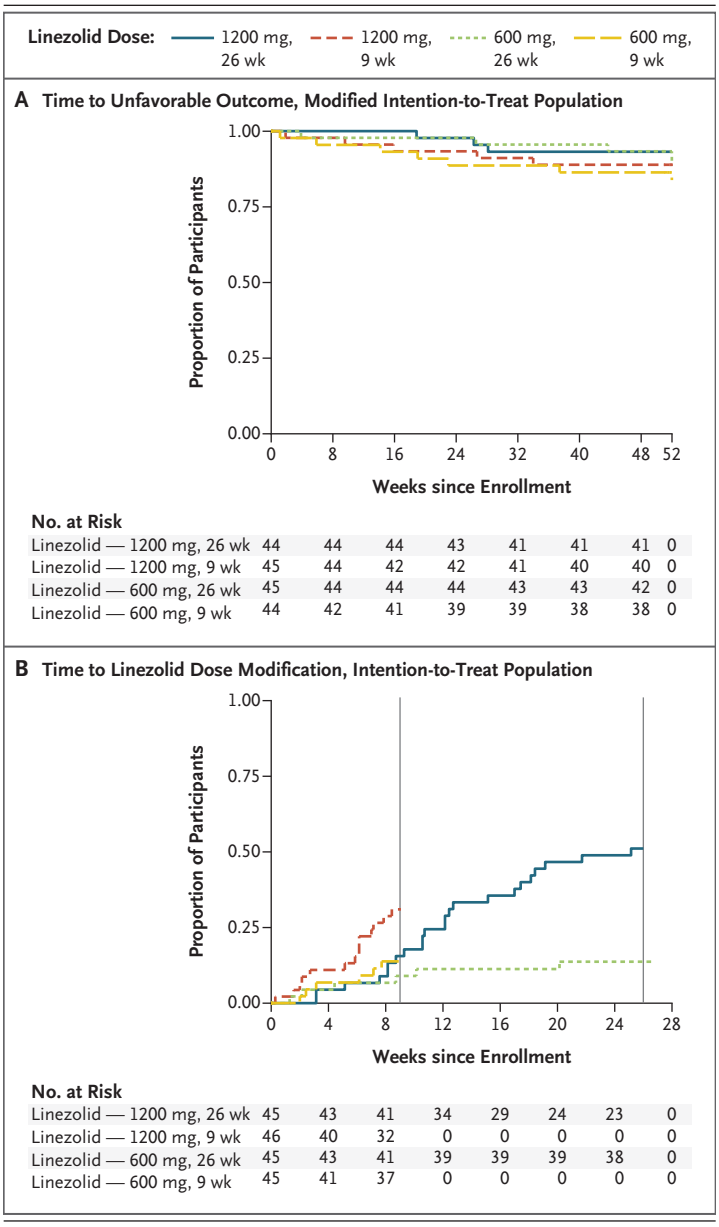

Figure 2. Time to an Unfavorable Outcome and Time to a Linezolid Dose Modification.

Panel A shows the time to an unfavorable outcome in the modified intention-to-treat population (i.e., the participants in the intention-to-treat population, with the exception of those who were lost to follow-up after successful treatment or who died from a cause that was adjudicated to be unrelated to tuberculosis). The intention-to-treat population was defined as all participants who underwent randomization, with the exception of those who were excluded after the randomization period either because of protocol violations that occurred before randomization (and were detected after randomization) or because they did not have drug-resistant tuberculosis that was confirmed on the basis of a sputum sample obtained within 3 months before screening. There were no exclusions from the intention-to-treat population. An unfavorable outcome was defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. In participants with bacteriologic failure, a negative culture status for *Mycobacterium tuberculosis* was not attained or maintained during treatment. In those with relapse, negative culture conversion status was not maintained during follow-up, and a positive culture of an *M. tuberculosis* strain was confirmed as being genetically identical to that at baseline. Clinical treatment failure was defined as a change from the protocol-specified tuberculosis treatment as a result of a lack of clinical efficacy, retreatment for tuberculosis, or tuberculosis-related death. Panel B shows the time to a linezolid dose modification (i.e., the first of interruption, reduction, or discontinuation) in the intention-to-treat population through the last dose of linezolid. The vertical lines represent the time of the last active linezolid dose.

received linezolid for 9 weeks, which suggests that participants who receive linezolid for a shorter duration may be more vulnerable to treatment failure. These findings also serve to highlight the need for drug-susceptibility testing and for the continued improvement of treatment regimens.[17]

Peripheral neuropathy is one of the most commonly observed side effects of linezolid. Risk factors for the development of neuropathy include the duration and dose of linezolid treatment, coexisting conditions, nutritional status, the use of concurrent medications, and possibly genetic factors.[18-21] The higher incidence of peripheral neuropathy reported among South African participants than among those in Georgia, Moldova, or Russia was notable, but no explanatory factors could be identified, including HIV status, and this finding warrants further research.

This trial has several limitations. First, the trial size limits the precision of any estimate of treatment effect. Second, the lack of a standard-care control group means there is no clear comparator against which the observed efficacy can be assessed. In that regard, it is reassuring that the observed efficacy is consistent with that in the Nix-TB study.

This randomized, dose-blind trial of alterna-

Table 3. Safety Analysis.*

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0
≥1 Episode of optic neuropathy†‡	4 (9)	0	0	0	4 (2)
≥1 Episode of peripheral neuropathy‡§	17 (38)	11 (24)	11 (24)	6 (13)	45 (25)
Severity of event in participants with ≥1 episode of peripheral neuropathy§¶					
Grade 1	10 (22)	7 (15)	10 (22)	6 (13)	33 (18)
Grade 2	7 (16)	4 (9)	1 (2)	0	12 (7)
≥1 Episode of myelosuppression‖	10 (22)	7 (15)	1 (2)	3 (7)	21 (12)
Hemoglobin level					
<8 g/dl and below baseline level	0	1 (2)	0	0	1 (1)
<25% below baseline level	9 (20)	4 (9)	0	0	13 (7)
Absolute neutrophil count <750/mm^3 and below baseline level	1 (2)	3 (6)	1 (2)	3 (7)	8 (4)
Platelet count <50,000/mm^3 and below baseline level	0	0	0	0	0
Liver-related serious adverse event	0	1 (2)	1 (2)	1 (2)	3 (2)
QTcF interval >60 msec above baseline value	0	2 (4)	0	1 (2)	3 (2)
Maximum QTcF interval ≥500 msec	0	1 (2)	0	1 (2)	2 (1)
Any interruption, dose reduction, or discontinuation of linezolid	23 (51)	14 (30)	6 (13)	6 (13)	49 (27)

* All participants who received at least one dose of a trial medication were included in the safety analysis population. Listed are adverse events that occurred from the start of treatment through 14 days after the end of treatment. QTcF denotes corrected QT interval calculated with Fridericia's formula.

† The incidence of optic neuropathy was evaluated with the use of the standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query, which included the preferred term optic nerve disorder.

‡ These adverse events were coded with the use of MedDRA, version 23.0.

§ The incidence of peripheral neuropathy was evaluated with the use of the standardized MedDRA query, which included the preferred term peripheral neuropathy.

¶ The highest grade was reported for participants with at least one event that occurred from the start of treatment through 14 days after the end of treatment.

‖ Myelosuppression was determined on the basis of laboratory results.

tive linezolid regimens in bedaquiline–pretomanid–linezolid treatment showed favorable cure rates of the bedaquiline–pretomanid–linezolid regimen among participants with highly drug-resistant tuberculosis, inclusive of XDR, pre-XDR, and rifampin-resistant tuberculosis that

had not responded to treatment or for which a second-line regimen had been discontinued because of side effects. In addition, lower linezolid doses resulted in fewer toxic effects than the 1200-mg, 26-week regimen. A 600-mg, 26-week regimen of linezolid appeared to have the most favorable risk–benefit profile among the regimens studied.

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APPENDIX

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